REVIEW ARTICLE

Causes and Early Diagnosis of Vitamin B_{12} Deficiency

Wolfgang Herrmann, Rima Obeid

SUMMARY

Introduction: Vitamin B_{12} deficiency is widespread. Among the population groups at risk are older people, vegetarians, pregnant women, and patients with renal or intestinal diseases. The neurological symptoms of vitamin B_{12} deficiency are unspecific and can be irreversible. Early detection is therefore important, using the most sensitive and specific markers available.

Methods: Selective literature review.

Results and discussion: Total serum vitamin B_{12} is a late, relatively insensitive and unspecific biomarker of deficiency. Holotranscobalamin (holoTC), also known as active B_{12}, is the earliest laboratory parameter for B_{12} deficiency, while methyl malonic acid (MMA) is a functional B_{12} marker that will increase when the B_{12} stores are depleted. Isolated lowering of holoTC shows B_{12} depletion (negative B_{12} balance), while lowered holoTC plus elevated MMA and homocysteine indicates a metabolically manifest B_{12} deficiency, although there still may be no clinical symptoms. The diagnostic use of holoTC allows treatment to be instituted before irreversible neurological damage occurs. As the first clinical manifestations of vitamin B_{12} deficiency are unspecific, those at risk should have their B_{12} status checked regularly, every two to three years. Because no randomized controlled trials have yet been completed, the diagnostic and therapeutic measures proposed here are merely recommendations.

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Key words: vitamin B_{12}, neurological diagnosis, diagnosis, treatment concept, homocysteine

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Vitamin B_{12} deficiency is more widespread in the population than has been assumed so far (1, 2). Since a deficiency in this vitamin can lead to irreversible neurological damage, early diagnosis is essential (3, e1, e2). In recent years, new and sensitive diagnostic markers to determine a person's vitamin B_{12} status have become available. It is therefore important to review the suitability of vitamin B_{12} as a marker for the vitamin B_{12} status. This article describes causes and effects of vitamin B_{12} deficiency and presents the currently available laboratory markers for diagnosing vitamin B_{12} deficiency disease.

Research into vitamin B_{12} (cobalamin) started in 1926, when George Minot and William Murphy discovered that pernicious anemia can be treated by including vast amounts of liver in patients' meals. Vitamin B_{12} is synthesized exclusively in micro-organisms, and in humans it is an essential component in methyl group transfer and cell division. The vitamin is crucially involved in the proliferation, maturation, and regeneration of neural cells. In combination with folic acid, as an enzymatic essential cofactor in the metabolism of homocysteine, vitamin B_{12} maintains low homocysteine levels.

Methods

This review article is based on a selective literature search. The authors searched PubMed using the following search terms: "diagnosing vitamin B_{12} deficiency," "symptoms of vitamin B_{12} deficiency," "metabolic markers of vitamin B_{12} deficiency." The authors used acknowledged references for their scientific and clinical work.

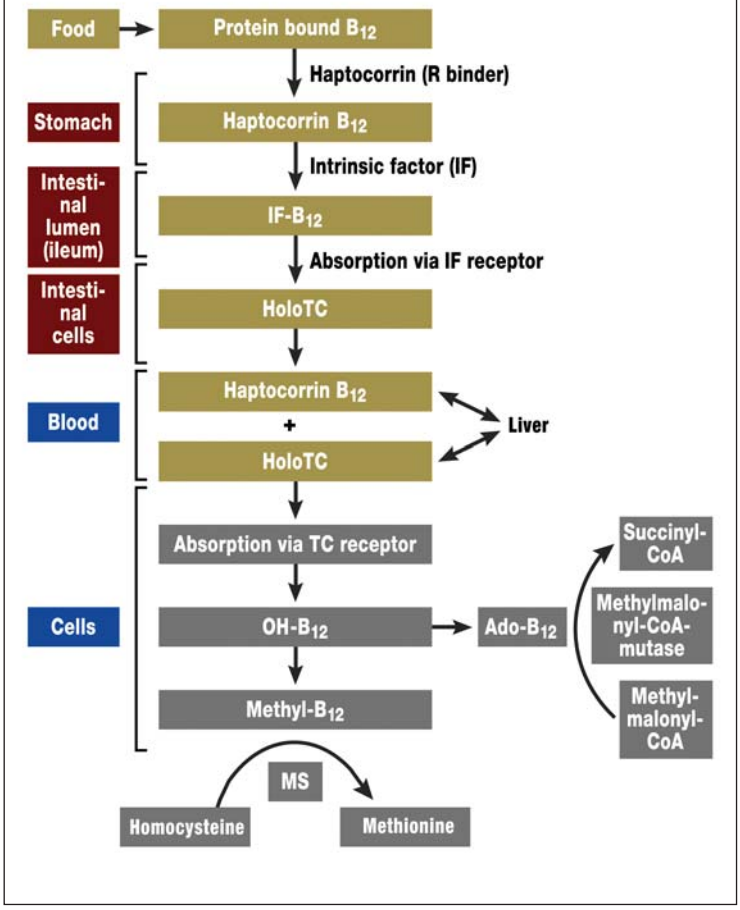
Results and discussion

Transport and metabolic function of vitamin B_{12}

On the one hand, vitamin B_{12} is a cofactor of L-methylmalonyl-CoA-mutase; as desoxyadenosylcobalamin it is involved in the isomerization of L-methylmalonyl-CoA to succinyl-CoA. On the other hand, as methylcobalamin it is a cofactor for methionine synthase (e3). This enzyme transfers a methyl group of 5-methyltetrahydrofolate to homocysteine during the synthesis of methionin. In case of intracellular deficiency of cobalamin, plasma concentrations of methyl malonic acid (MMA) and homocysteine will rise.

Vitamin B_{12} from food is made available through pepsin and gastric acid. It binds to R-binder (haptocorrins)

FIGURE 1



Transport and cellular absorption of vitamin B_{12}

B_{12}, vitamin B_{12}; TC, transcobalamin II; MS, methionine synthase; Ado, desoxyadenosyl

and is transferred to the intrinsic factor (IF) in the intestinal lumen by means of a pH dependent process. In the terminal ileum, the IF-B_{12} complex binds to IF receptors on the membrane surface of enterocytes and is then transferred through the ileal membrane. Vitamin B_{12} is subsequently released in the enterocytes and transferred to transcobalamin II (TC) *(figure 1)*. The B_{12}-TC complex—known as holotranscobalamin (holoTC)—arrives in the blood circulation and circulates until it is taken up by the cells. A maximum of 30% of circulating B_{12} is bound to TC, which represents metabolically active B_{12}. The vitamin B_{12} that is bound to haptocorrin is thought to transport the surplus of vitamin B_{12} to the liver.

Modern biomarkers for metabolic vitamin B_{12} deficiency

Total vitamin B_{12} measurement is used cost effectively as the parameter of choice, but it has limited sensitivity and specificity, especially in persons with vitamin B_{12} concentrations <400 pmol/L (4, e4). If the total vitamin B_{12} concentration is in the lower reference range, 156 to 400 pmol/L, vitamin B_{12} deficiency cannot be ruled out. Clinical signs of vitamin B_{12} deficiency can be seen in persons with vitamin B_{12} concentrations within the reference range (>156 pmol/L) (5). Persons with normal concentrations of vitamin B_{12} may have raised concentrations of MMA (>300 nmol/L) and lowered concentrations of holoTC (<35 pmol/L), owing to intracellular, metabolically manifest (functional) vitamin B_{12} deficiency (4). By contrast, lowered concentrations of B_{12} and normal MMA indicate a false positive finding.

A lowered serum holoTC concentration is the earliest marker of vitamin B_{12} deficiency and signals that the body does not have sufficient available vitamin B_{12} and that the B_{12} stores are emptying as a result of the negative balance of B_{12} (4). At this stage, clinical or hematological symptoms might not yet be present.

Lowered holoTC combined with raised MMA and homocysteine levels are indicative of metabolically manifest vitamin B_{12} deficiency. Clinical signs may already be present but can still be missing—the patient may therefore still be clinically inconspicuous (6). Metabolically manifest B_{12} deficiency can affect the bone metabolism, for example, and stimulate osteoclasts (7). The exact prevalence of clinically significant B_{12} deficiency is not known; the range of symptoms is wide and the new markers enable the detection of vitamin deficiency notably more often.

Measuring MMA is expensive and requires special equipment, such as mass spectrometers. The holoTC immunoassay is available as an automated test. The costs are about double that of total vitamin B_{12}. With regard to the cost-benefit effect of early detection of vitamin B_{12} deficiency by using holoTC, this test will become established as the laboratory parameter of choice to measure vitamin B_{12} status.

No consensus exists with regard to screening for vitamin B_{12} deficiency. Screening makes sense when first signs of B_{12} deficiency can be detected before neurological or hematological anomalies develop. For this reason, only the modern biomarkers, such as holoTC and MMA, are suitable screening tools. Although holoTC is a very early marker and MMA a functional biomarker for vitamin B_{12} deficiency, there is no universal marker for vitamin B_{12} status because limitations exist with regard to their diagnostic informative value *(figure 2)*.

Development and clinical presentation of vitamin B_{12} deficiency

Insufficient intake or disrupted absorption of vitamin B_{12} will result in vitamin B_{12} deficiency. According to the recommended dietary intake (RDI) guidelines from the National Research Council of the US National Academy of Sciences, adults should ingest 2.4 µg daily, pregnant women up to 6 µg (8). The calculation of the required amount is based on the calculation of the amount of vitamin B_{12} that is necessary to sustain a normal hematological status (normal hemoglobin and mean corpuscular volume of erythrocytes [MCV]) and to maintain remission in pernicious anemia. At the time when the recommended dietary intake was set, no studies had investigated the direct link between vitamin B_{12} intake

and MMA concentrations. New data have shown that the plasma concentration of MMA and homocysteine falls when vitamin B_{12} is ingested, whereas the holoTC concentration rises (9). A minimum daily intake of 6 µg vitamin B_{12} results in an optimal plasma concentration of the investigated biomarkers (9). More recent studies have shown that the recommended daily intake of B_{12} should be newly determined and seems too low, especially for older people.

Vitamin B_{12} is important for DNA synthesis, and formation and maintenance of myelin sheaths, the synthesis of neurotransmitters, and erythropoiesis. Clinical vitamin B_{12} deficiency has two main manifestations: hematological and neuropsychiatric disorders. Symptoms often develop before a shortfall on the lower B_{12} reference limit (6). Macrocytic anemia is regarded as a late indicator of vitamin B_{12} deficiency.

The macrocytosis caused by B_{12} deficiency can be masked by concomitant iron deficiency, and the diagnosis is thus difficult (e5). Iron deficiency related microcytosis dominates over B_{12} deficiency related macrocytosis if the iron deficiency is more severe than the B_{12} deficiency (e6). The B_{12} deficiency can cause an additional loss of iron by means of a secondary effect on the enterocytes (e6).

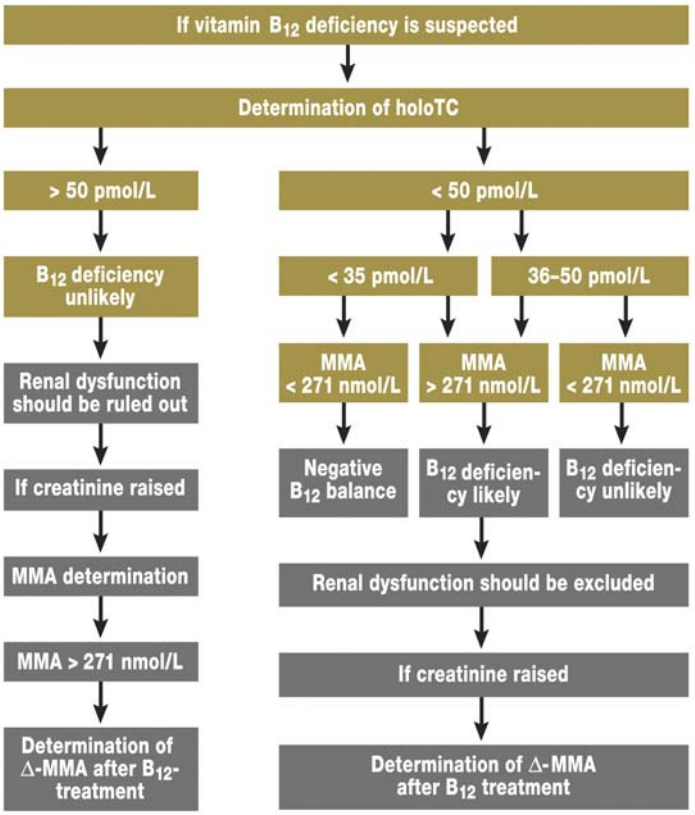
Large vitamin B_{12} stores exist in the body, which is why a deficiency will become evident only after many years. In general, vitamin B_{12} deficiency develops in several stages:

- Depletion of stores
- Metabolic-functional disorder
- Clinical manifestation.

Hyperhomocysteinemia in vitamin B_{12} deficiency is important as an atherogenic risk factor but also as a sign of hypomethylation—for example, of DNA, RNA, myelin, phospholipids, or neurotransmitters. Hypomethylation occurs subsequent to the reduced availability of S-adenosyl-methionine (SAM), which is a universal methyl group donor. Vitamin B_{12} deficiency inhibits methionine synthase. The result is reduced methionine synthesis, with subsequent lowering of the SAM concentration. Funicular spinal cord disease (myelosis) is a common neurological sequela of vitamin B_{12} deficiency. The psychiatric and neurological disorders and the cognitive disorders, depression, or dementia that are observed in vitamin B_{12} deficiency can precede hematological anomalies by years, and sometimes such anomalies do not even develop.

Morphological changes to blood and bone marrow cells are among the main symptoms of vitamin B_{12} deficiency. Because of their high cell turnover rate, hematopoiesis reacts rapidly and sensitively to the blocked nucleic acid metabolism. Megaloblastic anemia in vitamin B_{12} deficiency develops as a result of disrupted DNA synthesis and the resultant maturation disorder of the cell nucleus, whereas the cytoplasm develops normally. In the periphery, macrocytic erythrocytes (MCV >110 fl) and hypersegmented neutrophils can be observed.

FIGURE 2



Algorithm for laboratory diagnosis of vitamin B_{12} deficiency. Δ-MMA is the reduction of methyl malonic acid (MMA) concentration subsequent to injections of vitamin B_{12} by more than 200 nmol/L. (The chart is our own suggestion for the early diagnosis of vitamin B_{12} deficiency; thus far, no consensus exists to what extent applying the above criteria helps to avoid neurological complications of vitamin B_{12} deficiency.)

Risk groups

The prevalence of subclinical functional vitamin B_{12} deficiency is higher than hitherto assumed when sensitive and relatively specific markers are used—such as MMA, holoTC, and homocysteine (10, 11). Risk groups for vitamin B_{12} deficiency include *(table)*

- patients with unexplained anemia;
- patients with unexplained neuropsychiatric symptoms;
- patients with gastrointestinal manifestations, including stomatitis, anorexia, and diarrhea;
- elderly people (11);
- vegetarians (4);
- patients with gastrointestinal disorders, such as Crohn's disease or infection with Helicobacter pylori, or patients with stomach resection (12).

The rate of people in the risk population who will develop clinical symptoms because of vitamin B_{12} deficiency has thus far not been studied systematically.

TABLE

Risk populations with high frequency of vitamin B_{12} deficiency, who should be tested at regular intervals (every 2 to 3 years)

Group	Causes and remarks
Vegetarian, vegan, and macrobiotic diet	Low vitamin B_{12} intake
Neonates and breast-fed infants of vegetarian mothers	Low vitamin B_{12} absorption with breast milk
Elderly people	Pernicious anemia, achlorhydria, malabsorption caused by gastrointestinal disorders (gastric or intestinal surgery, gastritis, Helicobacter pylori, atrophy, bacterial overgrowth of the intestine, alcohol)
Neurodegenerative and neuropsychiatric disorders	Neuropathies, dementia, Alzheimer's disease, cognitive disorders, schizophrenia
Chronic atrophic corpus gastritis	Malabsorption of vitamin B_{12}; Crohn's disease
Disorders of the terminal ileum	Ileal lymphoma, ileal resection, bacterial overgrowth of the ileum
Macrocytic anemia	Low absorption of vitamin B_{12} or pernicious anemia
Chronic alcoholism	Low or disrupted absorption of vitamin B_{12}
Medication	Proton pump inhibitors, H_2 receptor agonists, inhalation of nitrous oxide
AIDS associated myelopathy	Abnormal, vitamin B_{12} dependent transmethylation

In the population, the prevalence of vitamin B_{12} deficiency in younger people is 5% to 7% (e7, 13). Functional vitamin B_{12} deficiency—that is, raised MMA and lowered holoTC—is common in old age and has been diagnosed in 10% to 30% of patients older than 65 years of age (10, 11, 14). A high prevalence of a slightly abnormal vitamin B_{12} status has been reported in elderly people, despite intake of the recommended daily dose (> 2.4 µg/day). This deficiency is not presumed to be associated with dietary causes but with malabsorption (15). 53% of elderly patients from Strasbourg who had vitamin B_{12} deficiency had malabsorption problems, 33% had pernicious anemia; in only 2% was vitamin B_{12} deficiency related to insufficient dietary intake, and in 11% the etiology of the vitamin B_{12} deficiency remained unexplained (16). However, because the currently recommended dietary intake for vitamin B_{12} in elderly people is low, dietary deficiencies are underdiagnosed.

Using synthetic B_{12} preparations can protect elderly persons from symptoms of deficiency (e8, 17). Dietary intake of B_{12}, however, does not provide any information on the vitamin B_{12} status because malabsorption is a common and important factor. Further, elderly persons often have atrophic gastritis, pernicious anemia, or achlorhydria. Disorders that affect the gastrointestinal pH can also result in malabsorption and thus vitamin B_{12} deficiency. The incidence of Helicobacter pylori is high in elderly people and can lead to atrophic gastritis, and in turn to B_{12} malabsorption, owing to disrupted production of hydrochloric acid (1). Helicobacter pylori was found in 56% of patients with vitamin B_{12} deficiency (18). In 40% of patients, serum concentrations of B_{12} rose after treatment for Helicobacter pylori infection. According to recent reports, longer term treatment of Helicobacter pylori (1 year) resulted in a significant rise in mean vitamin B_{12} (from 146 pmol/L to 271 pmol/L) and a fall in mean homocysteine concentrations (from 41 µmol/L to 13 µmol/L) (19). B_{12} malabsorption owing to Helicobacter pylori infection can thus lead to vitamin B_{12} deficiency and hyperhomocysteinemia (e9).

Vegetarians are at high risk of developing vitamin B_{12} deficiency because animal products are the main sources of B_{12}. A functional B_{12} deficiency (lowered holoTC, raised MMA and homocysteine) is common in vegetarians and depends on the strictness of the diet and how long the vegetarian diet has been followed. A study of lacto-vegetarians and ovo-lacto-vegetarians found raised MMA in 63% of subjects (>271 nmol/L), lowered holoTC concentrations (<35 pmol/L) in 73% , and hyperhomocysteinemia (>12 µmol/L) in 33%. In vegans, raised MMA was found in 86%, lowered holoTC in 90%, and hyperhomocysteinemia in 55% (4).

Persons with an increased vitamin requirement are a further risk group for B_{12} deficiency—for example, pregnant and breast feeding women, patients with autoimmune disorders, or persons with HIV infection. Persons who regularly take proton pump inhibitors can also develop vitamin B_{12} deficiency.

B_{12} deficiency is also widespread in patients with renal disorders (20). In spite of normal plasma concentrations of vitamin B_{12} or holoTC, these patients often have raised serum concentrations of MMA and homocysteine (20). These can be corrected with vitamin B_{12} substitution, which indicates a deficiency before starting treatment (20). The likely cause is a disrupted cellular absorption of holoTC, which results in intracellular vitamin B_{12} deficiency and raised metabolites. Studies have shown that patients with renal disorders may have higher concentrations of holoTC, which seems to contradict B_{12} deficiency (20, 21). This can be explained with the role of the kidney in transcobalamin filtration and resultant secondary accumulation of holoTC. The plasma concentration of holoTC in such

Key messages

- Subtle, clinically inconspicuous vitamin B_{12} deficiency that has not yet been confirmed with a laboratory test is common in the general population. Clinical manifestations of B_{12} deficiency range from early neurological symptoms to hematological symptoms.
- Holotranscobalamin (holoTC) and methyl malonic acid (MMA) have higher sensitivity and specificity, compared with vitamin B_{12} determination, and are therefore regarded as modern biomarkers of B_{12} status. Total vitamin B_{12} as a marker results in underestimation of the prevalence of B_{12} deficiency.
- Early diagnosis of vitamin B_{12} deficiency is advisable because neurological symptoms may be irreversible and often occur before or without hematological manifestations.
- Patients with neurological symptoms of unknown etiology should be tested for B_{12} deficiency and malabsorption. A low intake of vitamin B_{12}, malabsorption, pernicious anemia, and gastrointestinal disorders with a shift in pH should be considered in the diagnosis and treatment of vitamin B_{12} deficiency.
- It has been shown in randomized studies that oral B_{12} substitution in persons with normal absorption is effective and improves neurological and hematological symptoms. The treatment should be controlled by determining a person's B_{12} status.

patients therefore does not reflect the functional vitamin B_{12} status correctly. A reduction of the MMA by more than 200 nmol/L after B_{12} injection confirms pretreatment deficiency. Since patients with renal disorders may have raised MMA concentrations that are not associated with vitamin B_{12} deficiency, B_{12} deficiency can be determined only by therapeutic lowering of MMA (20).

Treatment

The treatment of vitamin B_{12} deficiency depends on the underlying causes. Blocked or reduced oral bioavailability, such as occurs in pernicious anemia, requires injections of vitamin B_{12}. If, however, there are no obvious reasons for an injection, oral substitution is a sensible strategy.

Vitamin B_{12} supplementation can be used for treatment or prevention depending on whether a person is at risk or already affected. In long standing vitamin B_{12} deficiency, dietary modifications are not sufficient; these patients require longer term B_{12} supplementation to normalize their metabolism (e10). Vegetarians and older persons receiving oral vitamin B_{12} supplementation (10 to 500 µg) have been shown to have lower concentrations of MMA and higher holoTC and B_{12} concentrations than persons not receiving supplementation. This indicates the metabolic efficacy of oral supplementation (4, 22). In randomized studies in elderly patients, a daily intake of 1 to 2 mg cyanocobalamin have resulted in normalization of the metabolic signs of the B_{12} deficiency and in improved neurological symptoms—e.g., in terms of memory power, gait, perception of vibrations, and paresthesias (6, 17). Vidal-Alaball et al. (23) have shown in randomized studies that compared with intramuscular application, high oral dosages of vitamin B_{12} (1 mg and 2 mg; daily at the start of treatment, then weekly, and later monthly) are of comparable efficacy in terms of improved hematological and neurological symptoms.

The therapeutic recommendations with regard to dosage and administration of B_{12} substitution treatment are divergent (24). In the United States, patients usually receive vitamin B_{12} injections of 1 mg daily in their first week of treatment. In the following month, they receive weekly injections and then monthly injections (25). In Denmark, patients receive injections of 1 mg cyanocobalamin weekly during the first month and every 3 months subsequently, or 1 mg hydroxycobalamin every other month (e11).

The optimal dose of B_{12} can be adjusted by testing B_{12} status in blood by means of laboratory parameters. Measuring homocysteine and MMA concentrations is helpful in monitoring vitamin therapy (17). The homocysteine concentration provides information on whether the intracellular methionine cycle is functioning (which depends on B vitamins), whereas MMA documents specifically the effectiveness of B_{12} dependent reactions. Although overdosing does not result in adverse effects, overdosing of vitamin B_{12} should be avoided.

Conflict of interest statement
The authors declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

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